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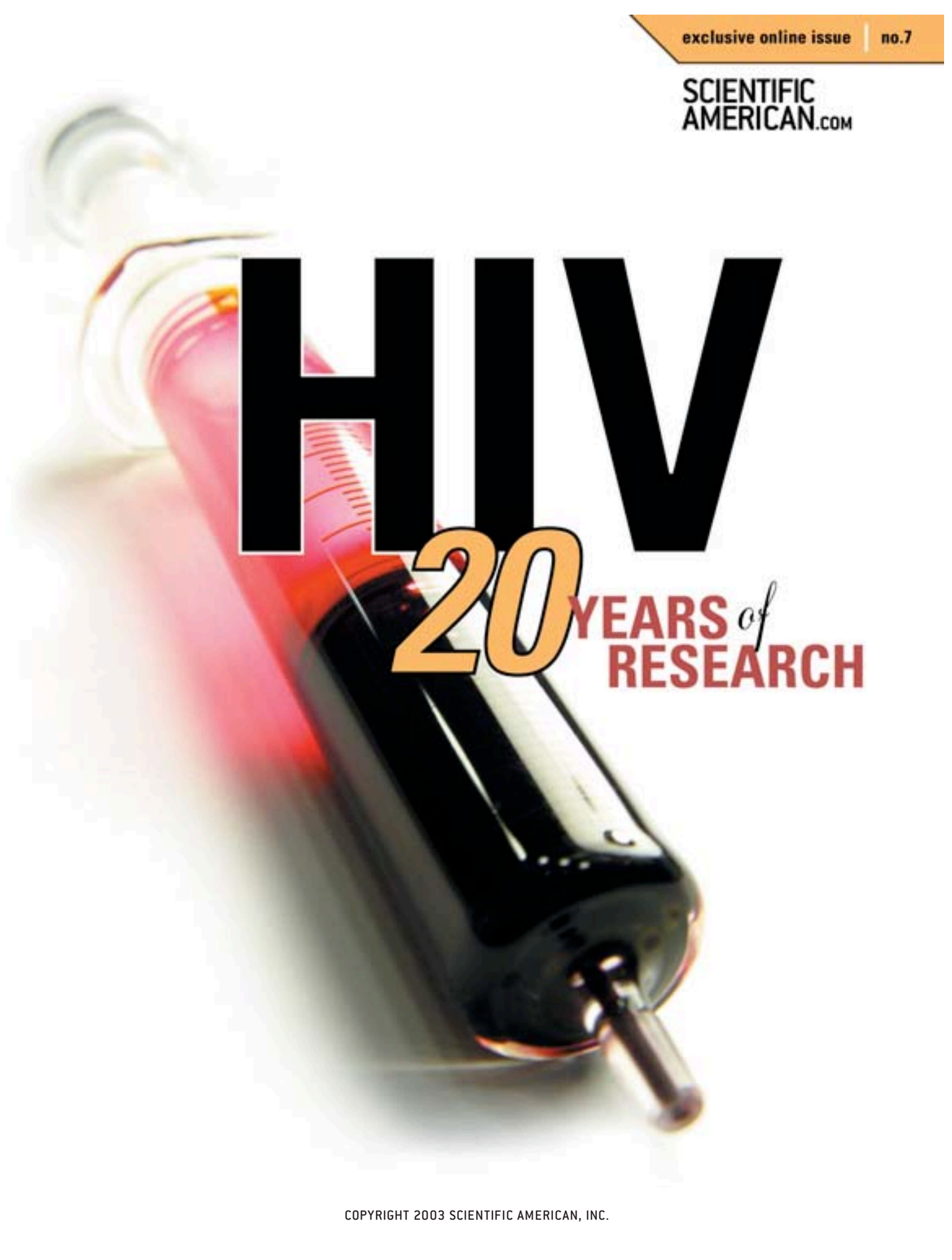

HIV

20 YEARS of RESEARCH

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HIV: 20 YEARS OF RESEARCH

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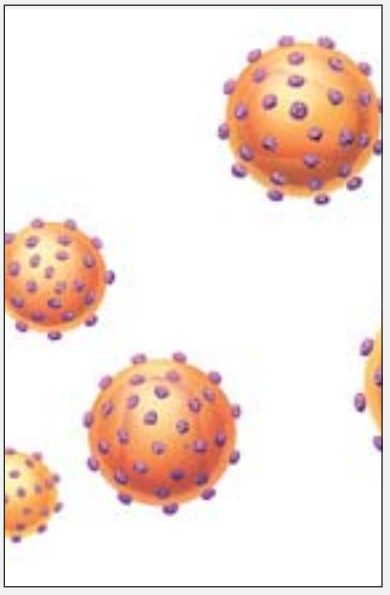

Nearly 20 years ago researchers first identified HIV as the cause for AIDS. Since then, scientists have made great strides in understanding how the virus operates and developing effective therapies. But the challenges to better treatment and prevention remain daunting. With 40 million people on the planet infected with HIV (more than three million died this past year alone), fresh insights can't come fast enough.

Scientific American has regularly covered advances in HIV research. In this anthology of articles published over the past decade, researchers share their expertise on how HIV wreaks havoc on the body, how the government might stem the HIV epidemic among drug users who inject their habit, and what sorts of treatments the future might bring. The authors discuss the search for AIDS-resistance genes and ponder the development of an HIV vaccine.

—The Editors

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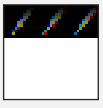
2 
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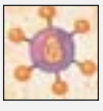
20 
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than 200 cells per microliter of b
cells are a form of white blood ce
mally, help the body protect itsel
fection.) This criterion provides
tive to diagnosing AIDS on the b
continually changing list of opportunisti
fections and malignancies.

There appear to be two predom
routes by which HIV is introduced
ulations of drug users. The first is
through overlapping, or bridge, gr
example, men who inject drugs a
have sex with men. This form of t
sion appears to have occurred in N
City, Rio de Janeiro and Sydney. T
is travel. Contrary to the stereot
injecting drug users, many travel
for business and pleasure. For ins
cent study found that 62 percent
users from Berlin had injected dru
their home city in the past two ye
cent of users from New York City ha
ed outside the area in the past tw

Once HIV has been introduced i
community of drug users, it can d
tremely quickly. Rapid increases
seroprevalence, or the percent of
who are infected, have been obs
both developed and developing
cities such as Bangkok, Edinburgh and
the Indian state of Manipur, HIV s
lence among drug users has risen
40 percent within two years or les

This fast transmission is freque
ated with certain kinds of behavi
of shooting galleries and of deal
Shooting galleries are places whe
jectors rent needles and syringes,
drugs through the skin and then r
equipment to the operator of the
rental to other customers. Paymen
in cash or in drugs. The term
works refers to the needles, syringes or
paraphernalia that a seller will offer to
one customer, take back and then lend to the
next.

Shooting galleries and dealers
serve several functions within the drug
culture. They provide a source of needles
and syringes, which are often scarce because
of legal restrictions. For instance,
most states have large populations of
such drug users require prescriptions for the
sale of needles and syringes. In many other
states and countries, over-the-counter sales
are permitted, but pharmacists are often
willing to sell to people they suspect of using
illegal drugs.

Shooting galleries allow drug us-
ers to avoid toting around equipment.
In almost all parts of the U.S., it is
illegal for people to possess equipment or
paraphernalia and places have taken on
ministering narcotics. In countries where
such possession is legal, many drug users are
reluctant to carry syringes because the police
often conclude that the individual is engaged

dealers
in illegal activities. Keeping needles clean
and current is one of these difficulties, and
the practice can provoke confrontations be-
tween the drug user and the people he or she
lives with.

At the same time that dealers and shooting galleries have served a profitable
purpose within the drug-using community,
they have also served as vectors for hepatitis
and other blood-borne infections. The injec-
tion devices are often shared by users who do not have any social contact
with one another and, therefore, do not
know another's HIV status or about
any risky behavior that they may engage in.
The materials are frequently used repeatedly
until the needle or syringe becomes dull or clogged with dried blood and is
discarded. With the advent of AIDS, dealers
have taken on a deadly aspect.

The reasons for the pervasiveness of injec-
tion as a form of illegal drug administration
are complex. Nevertheless, several features of
the practice are clear. During the first half of
the 20th century, the consumption of illicit drugs through injection was relatively rare out-
side the U.S. But as with parts of American
culture—from T-shirts and blue jeans to fa-
cial tissues—many different countries have adopted injection as a common practice.

The fact that cocaine, heroin and related drugs are illegal encourages the use of in-
jection. Before there were statutory restrictions greatly increasing the cost of illicit substances to
medical users. Injecting provides a way to
conceptualize. Injectable forms of opiates are
much more concentrated than traditional forms, such as opium or coca tea.
Injection provides an intense and economical
effect by maximizing the amount of drug that reaches the brain. People who sniff or
smoke drugs say that if they inject they use
only one third of the amount of the drug to maintain a habit.
Because the injectable forms of illicit drugs are concentrated, they are relatively sma

such shifts in behavior. Furthermore, act
HIV transmission has only seldom been used
as an end point in these studies.

Despite these methodological problems, we have found it possible to make a set of generaliza
tions with respect to developing effect
AIDS prevention programs. First, drug use
who inject are quite capable of learning
basic facts about HIV transmission and
about how to reduce exposure to the virus
indeed, one study found that 93 percent
the users of a particular methadone maint
nance center knew about AIDS, and 59 per-
cent had sought to protect themselve
against infection. Second, programs ar
more effective if they involve drug user
design and implementation. Third, programs
should provide the means for behavioral
change, including treatment for users wi
ing to limit or stop their use of drugs a
as access to sterile injection equipment
condoms. Fourth, people should be given
choices as to how they want to reduce t
chances of HIV transmission: there is no
solution that works for everyone. Finall
is apparent that to date no single progr
and no combination of programs have been
able to eliminate high-risk behavior co
pletely.

One point that emerges in an analysis
the programs is that their success appear
be a function of when they were implement
ed that is, whether they were established
when the HIV infection rate was minimal o
after HIV was entrenched in the community
We have recently analyzed the relatio
between AIDS prevention and risk behavior
in areas where HIV prevalence among drug
users is low. Holly Hagan of the Tacoma
Pierce County Health Department, David
Goldberg of the Communicable Diseases
Control Unit, Ruchill Hospital in Glasgow, Kerst
Tunving of the University of Lund and Alex
Wodak of St. Vincent s Hospital in Sydn
and their many colleagues provided info
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where HIV had been introduced into the popula-
tions of drug users. Yet seroprevalence amo
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1 percent) and stable for at least four yea
after introduction, AIDS prevention activiti
were limited, but all included communit
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Eliminating risky behavior was not neces-
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used by others. Most of the unsafe practi
appeared to be contained within small
groups of friends. Low and stable rates
HIV infection have also been reported i

volume and easier to ship. Indeed, much of the move-
ment of HIV can be traced along some drug
distribution routes. Once established in the AIDS risk reduction was reported by 80 percent of drug users in New York City, 84 percent in Glasgow, 82 percent in Tacoma, Wash. Anecdotal reports and similar attempts among laboratory animals and in cities and villages throughout the world. All these findings make it clear that drug users who inject often seek to reduce risk, but their success depends on whether they can obtain clean needles.

Prevention programs have also been designed to encourage behavioral changes on the part of drug users. Yet these services have not always received adequate political attention, or funding, because drug users are not at all concerned about their health. Fortunately, this attitude does not hold true for a great many of them.

In some cities, such as New York, drug users altered their behavior before any for-mal prevention program was implemented. Based on information obtained through the mass media and through the informal net-works of the drug subculture, they started to use illicitly obtained sterile needles. The reasons for this are complex and not entirely understood, but they probably include a perception that drug use is dangerous to health and that it is possible to quit. This assumption was based on another stereotype, that drug users are not at all concerned about their health. Fortunately, this attitude does not hold true for a great many of them.

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Athens, Toronto, Seattle, Perth
bourne. Thus, the experience of
cities studied may well be gen
many other places where preventi
were begun early.

In addition to cities where HI
rates were kept low, several te
searchers have observed declinir
new HIV infections and the stabilization
HIV seroprevalence in cities with se
prevalence. These findings come f
K. Watters of the University of C
San Francisco, Kachit Choopanya
Bangkok Metropolitan Administr
Roeland A. Coutinho of the Mu
Health Service of Amsterdam, Alf
colosi of the National Research
Milan and our group in New Yor
found, for instance, that HIV ser
in New York City has remained sta
1983. Stabilization, however, doe
a lack of new HIV infections. Ra
lization occurs when there is a r
between new infections and the lo
infected drug users through death
continuance of drug injection. I
ideal goal, but it does limit th
epidemic.

Whereas the studies suggest tha
sible to prevent or stabilize epi
such drug users, reversing a well
HIV epidemic is a much more for
task. The situation in Amsterdam offers a
good example of the difficulties encountered in
an entrenched HIV epidemic. HIV infection
prevalence among drug users in Amsterdam
had reached approximately 30 percent by
the mid-1980s.

Public health officials quickly mounted a
large AIDS prevention effort. This activity
included enlisting and funding the drug
users group to do prevention work, syringe
exchange, over-the-counter sales of needles
and syringes and drug abuse treatment on
demand. (It is
necessary to keep in mind one important
criticism of the Amsterdam AIDS prevention
program: many of the methadone main-
tenance clinics give methadone at dosages
that are too low to alleviate the symptoms of
drug withdrawal or craving.)

Coutinho and his colleagues reported
that the AIDS prevention pro-
grams in Amsterdam led to a sub-
stantial reduction in the frequency of unsafe injections.
The programs also brought about significant but smaller reductions in sexual activities. In addition, the rate of new HIV infections among drug users who inject declined from a peak of approximately eight per 100 person-years at risk during the early 1980s to a current rate of approximately four per 100 person-years at risk. This reduction in the rate of new infections is impressive, but the incidence is still much too high.

A high prevalence of HIV infection among drug users who inject drugs increases the risk for everyone in a community of drug users. An individual who is usually careful is more likely to be infected if, for example, he or she shares needles and injects with a needle that has been used by someone else. Sexual activity also becomes more dangerous, even though sexual activity is less effective in transmitting HIV than injecting drugs. If drug injection can be reduced by a large amount, or if individuals can be deterred from starting to inject drugs, the number of AIDS cases might be reduced in the future. (In areas where seroprevalence is high, as in the city of Edinburgh may have made the most progress in both these respects. The City Syringe Prevention Project there works with local general practitioners to administer drug abuse treatment mostly in the form of methadone. Recent research by Sally Closing Hours in societies that cannot make such equipment available to clinics and ho addicts is not likely. Household bleach has been used as a method for disinfecting, but intermittent studies fail to show any prot tively effective. Some of the difficulties may because needles and syringes need a relat long contact time to be disinfected t is, two rinsings, each for 30 seconds or longer.

The area also regions in which great knowledge of the dangers of drug injecti and sexual behavior is needed for prevent of transmission. Present programs appea for controlling HIV transmissio in low-seroprevalence areas, but a new ge

Despite the knowledge gathered from the studies described above as well as from ot research efforts, treatment and prevent programs for drug users have not been wid implemented. Three obstacles stand in the way. In some developing countries, the la of economic resources limits such preve tion as providing sterile injection equipme drug users in societies that cannot make such equipment available to clinics and ho addicts is not likely. Household bleach has been used as a method for disinfecting, but intermittent studies fail to show any prot tively effective. Some of the difficulties may because needles and syringes need a relat long contact time to be disinfected t is, two rinsings, each for 30 seconds or longer.

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eration of risk-reduction plans may be needed to reverse the situation in locations where seroprevalence is high. Among other components, these services would need to make sterile needles available, deter people from sharing injection equipment, offer drug abuse treatment and reduce the number of people who start to inject drugs. Encouraging the use of noninjectable forms of drugs has also been suggested as a way to prevent the transmission of HIV. But workable strategies for implementing this idea have not yet been developed.

The biggest obstacle to reducing the spread of HIV among drug users is neither a lack of resources nor a lack of knowledge but a lack of political will to utilize already existing information. Many of the strategies for preventing HIV infection have reasonable evidence for their effectiveness but remain highly politically charged. In Europe, programs that offer maintenance treatment have remained little tested, and that approach is not widely used. In some cities, such as Amsterdam, when methadone maintenance is permitted, it is provided at dosages that are known to be effective and for periods that are not too short. In other places, a user must be certified infected with HIV before he or she is permitted to receive methadone maintenance treatment.

In the U.S., and to a lesser extent in Sweden, syringe exchanges and over-the-counter sales of sterile injection equipment have remained very controversial. Opponents of legal access to such equipment have claimed that these programs would promote illegal drug injection and would be taken as an official social condoning of the behavior. Yet no one has found any evidence to support this contention. In the U.S., the debate over syringe exchange has been complicated by our historical tendency to stigmatize certain social groups for their illicit drug use, leading to public hostility to debate over AIDS prevention [see Opium, Cocaine and Marijuana in American History, by David F. Musto; SCIENTIFIC AMERICAN, July 1991].

Some of the opposition to syringe exchange, over-the-counter sales of injection equipment and other less dangerous injection programs does not consider research, or scientific evidence. In Sweden the government has ordered the findings of an evaluation study that called for the expansion of the existing syringe exchange plans into a national system. In the U.S., federal legislation prohibiting the funding of similar exchange services unless the surgeon general found such practices safe and effective. But until 1992 the federal government refused to fund research to examine the safety and effectiveness of locally funded efforts.

These counterproductive attitudes are slowly changing. The debate about methods to prevent AIDS among drug users has led to a general rethinking of how best to regulate the use of licit and illicit drugs. An approach called harm reduction has developed from work done in the Netherlands, the U.K. and Australia. The harm-reduction perspective openly acknowledges the difficulty of totally eliminating all misuse of psychoactive drugs. Nevertheless, it emphasizes the possibility of drastically reducing the individual and social harm associated with drug use.

Harm-reduction programs consider it possible to lower the chance of HIV infection among even persons who continue to take drugs, just as it is possible to reduce the chances of automobile accidents among persons who continue to drink alcohol. Harm-reduction programs are particularly compatible with scientific research on behavior, because such data are critical to determining which social policies work.

HIV infection among drug users who inject, their sexual partners and their children is now a global public health problem [see Understanding the AIDS Pandemic, by Roy M. Anderson and Robert M. May; SCIENTIFIC AMERICAN, May 1992]. It is very likely that the situation will continue to worsen as both drug use and HIV infection among users extends to more developing countries. Present risk-reduction strategies offer a good possibility for preventing the spread of HIV in places where HIV prevalence is low and where adequate resources for community outreach and sterile injection equipment are available. Actually reducing further HIV transmission among drug users, however, requires a political philosophy that enables officials to implement the findings of scientific research. So far, and at great cost, such enlightenment has eluded many governments.

Originally published in
August 1995

How HIV Defeats the Immune System

A plausible hypothesis suggests the immune devastation that underlies AIDS stems from continuous—and dangerous—evolution of the human immunodeficiency virus in the body

by Martin A. Nowak and Andrew J. McMichael

The interplay between the human immunodeficiency virus (HIV) and the immune system turns out to be significantly more dynamic than most scientists would have suspected. Recent research indicates that HIV replicates prodigiously and destroys many cells of the immune system each day. But this growth is met, usually for many years, by a vigorous defensive response that blocks the virus from multiplying out of control. Commonly, however, the balance of power eventually shifts so that HIV gains the upper hand and causes the severe immune impairment that defines full-blown AIDS.

We have put forward an evolutionary hypothesis that can explain the ultimate escape of the virus from immune control, the typically long delay between infection and the onset of AIDS, and the fact that the extent of this delay can vary considerably from patient to patient. Most infected individuals advance to AIDS over the course of 10 years or so, but some patients are diagnosed within two years of infection, and others avoid AIDS for 15 years or more.

We argue that the powerful immune response enabling many patients to remain healthy for years is finally undermined by continuous mutation of the virus. As will be seen, within any given individual, new viral variants may emerge that are able to evade the protective forces somewhat. In our view, the accumulation of many such variants can muddle the immune system to the point that it can no longer fight the virus effectively.

To understand how we came to this hypothesis, which is gaining clinical support, it helps to know a bit about how the immune system eradicates viruses in general and how it responds to HIV in particular. When any virus enters the body and colonizes cells, defensive forces launch a multipronged but highly targeted attack. Macrophages and related cells engulf some of the free particles and break them up. Then the cells fit certain protein fragments, or peptides, into grooves on proteins known as human leukocyte antigens (HLAs). The cells subsequently display the resulting complexes on their surface for perusal by the white blood cells called helper *T* lymphocytes.

The Body Fights Back

Each helper cell bears receptors able to recognize a single displayed peptide, or epitope. If it encounters the right epitope on a macrophage or similar cell, it binds to the peptide, divides and secretes small proteins. The proteins help to activate and promote replication of still other components of the immune system—notably cytotoxic, or killer, *T* lymphocytes and *B* lymphocytes.

Under the right circumstances, the killer *T* cells directly attack infected cells. Like macrophages, infected cells break up some viral particles, combine certain of the fragments with HLA molecules and exhibit the complexes on the cell surface. If a cytotoxic *T* lymphocyte, through its receptors, recognizes one of the epitopes on a diseased cell, it will bind to the epitope and destroy the cell before more viral particles can be generated. Activated *B* lymphocytes secrete antibodies that recognize specific peptides on the viral surface. The antibodies mark free viral particles, those not yet sequestered in cells, for destruction.

All these responses are believed to participate in the defense against HIV. In the initial stage of HIV infection, the virus colonizes helper *T* cells and macrophages. It also replicates unchecked for a while. As the amount of virus soars, the number of helper cells falls; macrophages die as well, but the effects on them have been less studied. The infected

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T cells perish as thousands of new viral particles erupt from the cell membrane. Soon, though, cytotoxic *T* and *B* lymphocytes mount a strong defense and kill many virus-infected cells and viral particles. These effects limit viral growth and give the body an opportunity to restore temporarily its supply of helper cells to almost normal concentrations. Nevertheless, the virus persists. In the early phase, which may last for a few weeks, about 30 percent of infected patients display some symptoms, often a fever that may be accompanied by a rash and swollen lymph glands. Even those individuals, though, usually go on to enter a prolonged symptom-free stage.

Throughout this second phase the immune system continues to function well, and the net concentration of measurable virus remains relatively low. Nevertheless, the viral level rises gradually, in parallel with a decline in the helper population. Accumulating evidence indicates that helper cells are lost because the virus and cytotoxic *T* cells destroy them, not because the body's ability to produce new helper cells becomes impaired. It is a sad irony that the killer cells required to control HIV infection also damage the helper *T* cells they need to function efficiently.

Patients are generally said to cross the line to AIDS when the helper cell count, which in healthy individuals measures 1,000 cells per microliter of blood, falls below 200. During this stage, the viral level climbs sharply, and measures of immune activity drop toward zero. It is the loss of immune competence that enables normally benign microorganisms (particularly protozoa and fungi) to cause life-threatening diseases in AIDS patients. Once AIDS develops, people rarely survive for more than two years.

Persistence of a good immune response in the face of constant attack by HIV raises the issue of why the immune system is unable to eradicate HIV completely in most, if not all, cases. Several years ago various features of HIV led one of us (Nowak) and his colleagues in the zoology department of the University of Oxford to suspect the answers lay with an ability of the virus to evolve in the human body.

Evolutionary Theory Predicts Trouble

Evolutionary theory holds that chance mutation in the genetic material of an individual organism sometimes yields a trait that gives the organism a survival advantage. That is, the affected individual is better able than its peers to overcome obstacles to survival and is also better able to reproduce prolifically. As time goes by, offspring that share the same trait become most abundant in the population, outcompeting other members—at least until another individual acquires a more adaptive trait or until environmental conditions change in a way that favors different characteristics. The pressures exerted by the environment, then, determine which traits are selected for spread in a population.

When Nowak and his co-workers considered HIV's life cycle, it seemed evident that the microbe was particularly well suited to evolve away from any pressures it confronted (namely, those exerted by the host's immune system). For example, its genetic makeup changes constantly; a high mutation rate increases the probability that some genetic change will give rise to an advantageous trait. This great genetic variability stems from a property of the viral enzyme reverse transcriptase. In a cell, HIV uses reverse transcriptase to copy its RNA genome into double-strand DNA. This DNA is inserted into a chromosome of the host, where it directs the production of more viral RNA and viral proteins. These elements, in turn, assemble themselves into viral particles that can escape from the cell. The virus mutates readily during this process because reverse transcriptase is rather error prone. It has been estimated that each time the enzyme copies RNA into DNA, the new DNA on average differs from that of the previous generation in one site. This pattern makes HIV the most variable virus known.

HIV's high replication rate further increases the odds that a mutation useful to the virus will arise. To appreciate the extent of HIV multiplication, consider findings released early this year from teams headed by George M. Shaw of the University of Alabama at Birmingham and by David D. Ho of the Aaron Diamond AIDS Research Center in New York City. The groups reported that at least a billion new viral particles are produced in an infected patient each day. They found that in the absence of immune activity, the viral population would on average double every two days. Such numbers imply that viral particles present in the body 10 years after infection are several thousand generations removed from the original virus. In 10 years, then, the virus can undergo as much genetic change as humans might experience in the course of millions of years.

A Scenario of Disease Progression

With knowledge of HIV's great evolutionary potential in mind, Nowak and his colleagues conceived a scenario they thought could explain how the virus resists complete eradication and thus causes AIDS, usually after a long time span. Their proposal assumed that constant mutation in viral genes would lead to continuous production of viral variants able to evade to some extent the immune defenses operating at any given time. Those variants would emerge when genetic mutations led to changes in the structure of viral peptides—that is, epitopes—recognized by the immune system. Frequently such changes exert no effect on immune activities, but sometimes they can cause a peptide to become invisible to the body's defenses. The affected viral particles, bearing fewer recognizable epitopes, would then become more difficult for the immune system to detect.

The hypothesis proposed that a mutation able to reduce recognition of an epitope would give a viral variant a survival advantage, at least until the immune system discovered and reacted to the altered peptide. This response would reduce the viral load for a time, but meanwhile other "escape mutants" would begin to break out, and the cycle would continue, preventing full elimination of the infection.

Such a scheme is extremely hard to verify with clinical tests alone, largely because the nonlinear interactions between the virus and the immune system are impossible to monitor in detail. Consequently, Nowak turned to a computer simulation in which an initially homogeneous viral population evolved in response to immunologic pressure. He reasoned that if the mathematical model produced the known patterns of HIV progression, he could conclude the evolutionary scenario had some merit.

The equations that formed the heart of the model reflected features that Nowak and his colleagues thought were important in the progression of HIV infection: the virus impairs immune function mainly by causing the death of helper *T* cells, and higher levels of virus result in more *T* cell death. Also, the virus continuously produces escape mutants that avoid to some degree the current immunologic attack, and these mutants spread in the viral population. After a while, the immune system finds the mutants efficiently, causing their populations to shrink. The model additionally distinguished between two kinds of immune responses: those recognizing epitopes that undergo mutation readily and those recognizing conserved epitopes (ones that appear in an unchanging form on every viral particle in the body, because the virus cannot tolerate their loss or alteration).

The simulation managed to reproduce the typically long delay between infection by HIV and the eventual sharp rise in viral levels in the body. It also provided an explanation for why the cycle of escape and repression does not go on indefinitely but culminates in uncontrolled viral replication, the almost complete loss of the helper *T* cell population and the onset of AIDS.

In particular, the model indicated that the immune system can often mount a strong defense against several viral variants simultaneously. Yet there comes a point, usually after many years, when there are too many HIV variants. When that threshold is crossed, the immune system becomes incapable of controlling the virus. This "diversity threshold,"

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as we call the breaking point, can differ from person to person. For instance, if the immune system is relatively weak from the start, a few variants may be sufficient to overcome the body's defenses.

There is an intuitive explanation for why the presence of multiple HIV variants in an individual can impair the efficiency of the immune system. This explanation considers the battle between HIV and the body's defensive forces to be a clash between two armies. Each member of the HIV army is a generalist, able to attack any enemy cell it encounters. But each member of the immune army is a specialist, able to recognize an HIV soldier only if the soldier is waving a flag of a precise color.

Suppose the armies would be equally powerful if every specialist in the immune army recognized the same flag and every HIV soldier carried that flag. Now suppose that the HIV army consisted of three groups, each carrying a different flag and that, in response, the immune specialists also divided into three groups, each recognizing a separate flag. Under these conditions, the immune army would be at a significant disadvantage. Any given immune specialist would recognize and attack only one out of every three enemy soldiers it encountered—the one carrying the right flag. The HIV soldiers, meanwhile, would continue to pick off every specialist they met and would ultimately win the war.

Predicting the Course of Disease

Beyond giving us the concept of a diversity threshold, the model offered a possible explanation for why some patients progress to AIDS more quickly than do others. If the initial immune response to conserved epitopes is strong, the efficiency of the defensive attack on HIV will not be undermined very much by mutation in other epitopes. (Many active members of the immune system will continue to recognize every infected cell or viral particle they encounter.) Hence, the body should control the virus indefinitely, in spite of quite high levels of viral diversity. In such individuals, progression to AIDS is likely to be slow (or may not happen at all).

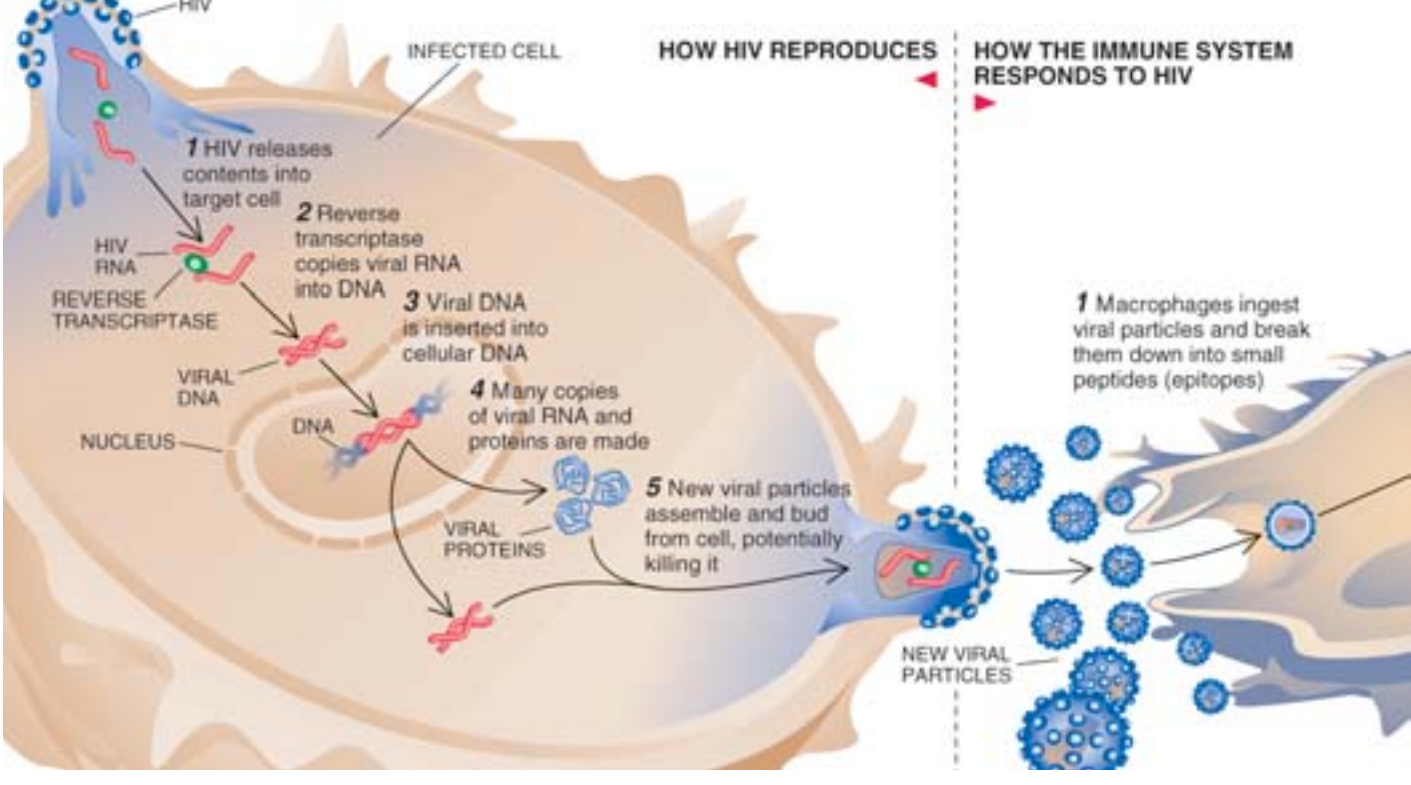
If the immune response to conserved epitopes is not strong enough to control the viral population on its own, but the combined effort of the responses against conserved and variable epitopes can initially manage the virus, the defensive forces could do well for quite a while. But the reaction against variable epitopes should eventually be undermined by the emergence of escape mutants and increasing viral diversity. In this case, HIV levels should rise as the response to variable epitopes becomes less efficient. This is the pattern that apparently occurs in most patients.

If the combined immune responses to conserved and variant epitopes are too weak to control HIV replication from the start, AIDS should develop rapidly. In that situation, the original viral particles would proliferate without encountering much resistance, and so the virus would be under little pressure to generate mutants able to escape immune reconnaissance. Such patients might progress to AIDS even in the absence of significant viral diversity.

The simulation also provided insight into probable properties of the viral population during each stage of HIV disease. In the earliest days, before the immune system is greatly activated, the viral variants that replicate fastest will become most abundant. Hence,

HIV versus the Immune System

The battle between HIV and the immune system begins in earnest after the virus replicates in infected cells and new particles escape (1–5, left). Rising levels of HIV in the body induce a response from many components of the immune system (right panel). Such responses can destroy free viral particles (1–5) as well as virus-infected cells (4a and 5a). But they generally are unable to eliminate HIV completely. One reason for the failure is that the virus infects, and depletes the levels of, helper T cells and macrophages, two central participants in the defense against HIV.



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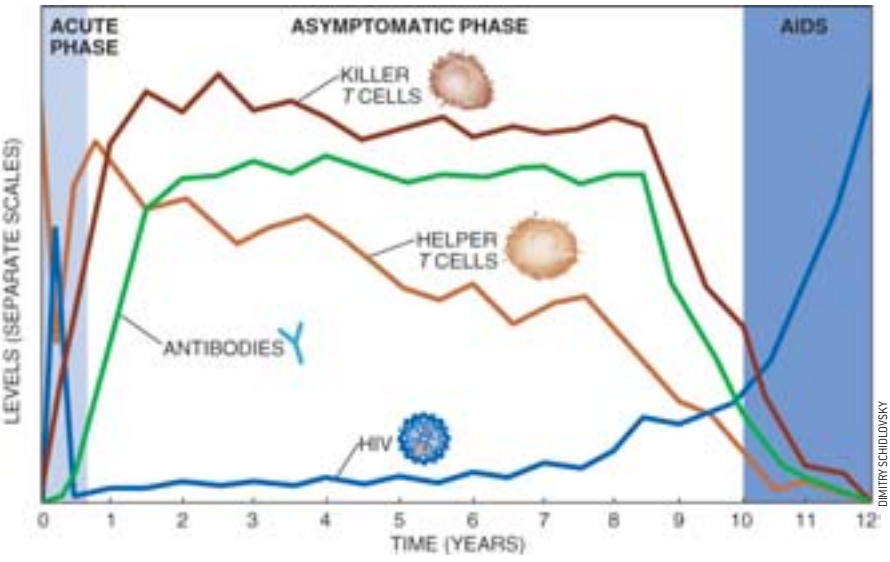
COURSE OF HIV INFECTION typically runs many years, during most of which the patient has no symptoms. Strikingly, the body's defenses—as indicated by levels of antibodies, killer *T* cells and helper *T* cells in the blood—remain strong throughout much of the asymptomatic period, eradicating almost as much virus as is produced. At some point, however, the immune defenses lose control of the virus, which replicates wildly and leads to collapse of the immune system.



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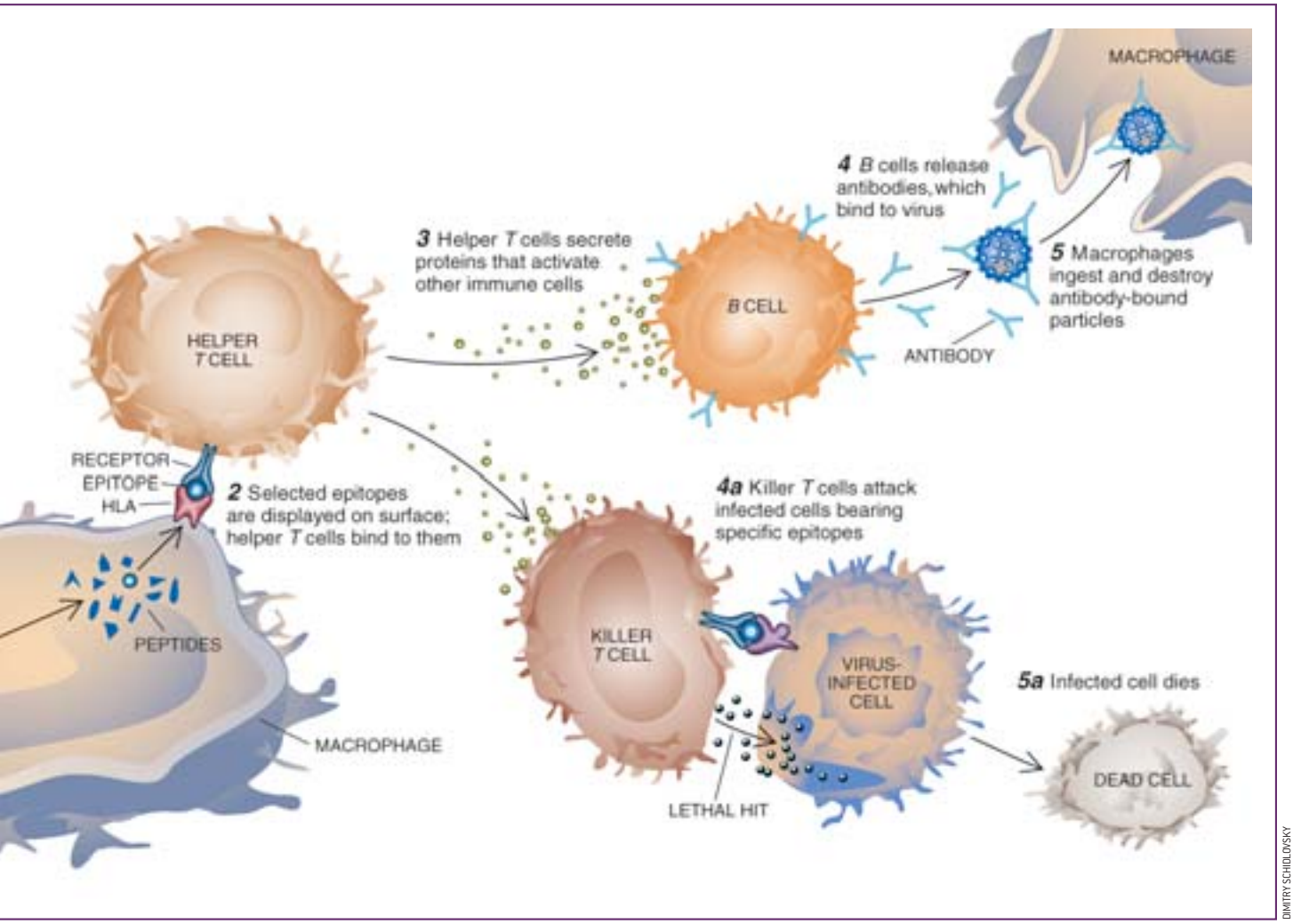
even if a patient were infected by several variants at once, after a short time most of the virus in the body would probably derive from the fastest-growing version. And so we expect little genetic diversity during the acute phase of disease.

After the immune system becomes more active, survival becomes more complicated for HIV. It is no longer enough to replicate freely; the virus also has to be able to ward off immune attacks. Now is when we predict that selection pressure will produce increasing diversity in epitopes recognized by immune forces. Once the defensive system has collapsed and is no longer an obstacle to viral survival, the pressure to diversify evaporates. In patients with AIDS, then, we would again anticipate selection for the fastest-growing variants and a decrease in viral diversity.

Long-term studies involving a small number of patients have confirmed some of the modeling predictions. These investigations, done by several researchers—including Andrew J. Leigh Brown of the University of Edinburgh, Jaap Goudsmit of the University of



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